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Comment on “On using a too large integration time step in molecular dynamics simulations of coarse-grained molecular models” by M. Winger, D. Trzesniak, R. Baron and W. F. van Gunsteren, *Phys. Chem. Chem. Phys.*, 2009, 11, 1934†

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In a recent study published in this journal, Winger *et al.*¹ investigate the magnitude of the time step to integrate the equations of motion in simulations with the coarse-grained MARTINI force field,² using an implementation³ of MARTINI in the GROMOS software.⁴ Based primarily on the drift in temperature and the magnitude of the energy fluctuations in bulk liquids, the authors conclude that a time step not exceeding 10 fs should be used to avoid artificial energy flow into or out of the system. In most applications of the MARTINI model to date, time steps of 20–40 fs have been used. Thus, the observation of Winger *et al.*¹ raises questions about possible artefacts caused by the apparent use of a too large integration time step. Although we appreciate the effort put into testing our model, we do not support the conclusions drawn.

First, the MARTINI force field is not an atomistically detailed force field. Many assumptions underlie the model, the major one being the neglect of some of the atomistic degrees of freedom. As a result, the interactions between particles are effective ones and the energy landscape is highly simplified. This simplified energy landscape allows for a greatly increased sampling speed at the cost of a loss of detail. This makes CG models in general so powerful.⁵ The emphasis, therefore, should not be to sample the energy landscape as accurately as possible, but rather, as effectively as possible. This is in contrast to traditional all-atom models, for which the energy landscape is more realistic and an accurate integration scheme is more important. In practice, the inherent ‘fuzziness’ of the MARTINI model makes the presence of artificial small energy sinks or sources a less critical problem than in accurate atomistic simulations. Most importantly, structural properties are very robust with respect to time step; Winger *et al.*¹ show that, even for the worst-case scenario (50 fs time step), there are no noticeable effects on structural properties of the systems investigated. Moreover, thermodynamic properties such as the free energy of solvation also appear insensitive to the size of

the time step. Thus, if the goal is to generate representative ensembles quickly, large time steps seem acceptable.

Secondly, using the standard GROMACS⁶ implementation of the MARTINI² model, we are unable to reproduce the results of Winger *et al.*¹ Analogous to the systems investigated by Winger *et al.*,¹ we simulated bulk water and hexadecane systems, both at NVE and NpT conditions. Our systems are composed of 1700 CG water particles or 800 hexadecane molecules. In the NVE set-up, the box volume was 205.5 nm³ (water) and 362 nm³ (hexadecane). For the NpT ensemble, weak coupling⁷ to a temperature bath ($T = 300$ K, coupling constant $\tau_T = 1$ ps) and pressure bath ($p = 1$ bar, $\tau_p = 5$ ps, compressibility 5×10^{-4} bar⁻¹) was used. The standard MARTINI protocol⁸ for the treatment of non-bonded interactions was followed, *i.e.* using the shifted potential Φ as implemented in GROMACS:

$$\Phi_{\alpha}(r) = \frac{1}{r^{\alpha}} - \frac{A}{3}(r - r_{\text{shift}})^3 - \frac{B}{4}(r - r_{\text{shift}})^4 - C;$$

$$r_{\text{shift}} \leq r \leq r_{\text{cut}}$$

$$\Phi_{\alpha}(r) = \frac{1}{r^{\alpha}} - C; \quad r \leq r_{\text{shift}}$$

$$A = \frac{\alpha\{(\alpha+1)r_{\text{shift}} - (\alpha+4)r_{\text{cut}}\}}{r_{\text{cut}}^{(\alpha+2)}(r_{\text{cut}} - r_{\text{shift}})^2}$$

$$B = -\frac{\alpha\{(\alpha+1)r_{\text{shift}} - (\alpha+3)r_{\text{cut}}\}}{r_{\text{cut}}^{(\alpha+2)}(r_{\text{cut}} - r_{\text{shift}})^3}$$

$$C = \frac{1}{r_{\text{cut}}^{\alpha}} - \frac{A}{3}(r_{\text{cut}} - r_{\text{shift}})^3 - \frac{B}{4}(r_{\text{cut}} - r_{\text{shift}})^4$$

Here α denotes the power of the respective LJ terms (6,12). Both potential and force are continuous and smoothly decay to zero between r_{shift} and the cut-off distance r_{cut} (see also the discussion in ref. 3). The MARTINI force field was parameterized using $r_{\text{shift}} = 0.9$ nm and $r_{\text{cut}} = 1.2$ nm, which we use in the current study. Two pairlist update schemes were compared; the first with an update frequency of $m_{\text{list}} = 5$ and a cut-off of $r_{\text{list}} = 1.4$ nm, the second with $n_{\text{list}} = 10$ and a cut-off of $r_{\text{list}} = 1.2$ nm. The first set-up is more accurate, but $\sim 30\%$ more expensive compared to the second set-up, which is usually applied. Additional simulations were performed with the shift parameters as used in the GROMOS

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† Electronic supplementary information (ESI) available: Detailed description of how the instantaneous and reported temperatures are calculated for the GROMOS, GROMACS, and CHARMM packages, and additional simulations showing that the observed temperature shifts are only apparent. See DOI: 10.1039/b915293h

Table 1 Properties for pure water and hexadecane systems in the NVE ensemble. Results obtained from 1.2 ns simulations, analyzed over the last 600 ps. Initial temperature was set to 300 K. The effect of time step dt , pairlist update frequency n_{list} , and pairlist cut-off r_{list} on selected properties (ensemble averages of the temperature T , and the ratio of the average fluctuations in total and potential energy $\Delta E^{\text{tot}}/\Delta E^{\text{pot}}$) is presented

dt/fs	n_{list}	$r_{\text{list}}/\text{nm}$	Water, NVE		Hexadecane, NVE	
			$\langle T \rangle/\text{K}$	$\Delta E^{\text{tot}}/\Delta E^{\text{pot}}$	$\langle T \rangle/\text{K}$	$\Delta E^{\text{tot}}/\Delta E^{\text{pot}}$
	10	1.2				
4			296	0.2	299	0.2
12			259	2	265	2
40 ^b			167	3	122	5
	5 ^a	1.4				
4			298	0.002	300	0.002
12			299	0.01	301	0.01
24			302	0.05	303	0.03
30			304	0.07	305	0.05
40			316	0.7	310	0.3
40 ^c			286	5	289	1.5

^a Similar results are obtained with $n_{\text{list}} = 10$, $r_{\text{list}} = 1.4$ and with $n_{\text{list}} = 1$, $r_{\text{list}} = 1.2$. ^b Freezing of water is observed. ^c GROMOS type implementation³ in which the potential is shifted between 0.0 and 1.4 nm.

implementation³ of MARTINI, *i.e.* $r_{\text{shift}} = 0$ nm and $r_{\text{cut}} = 1.4$ nm. All simulations were performed with GROMACS, version 3.3.1.⁶ Results are summarized in Table 1 (NVE) and Table 2 (NpT).

The NVE simulations show that, indeed, energy sinks or wells are present. At increasing time steps, the initial temperature is not maintained, and the fluctuations in the total energy become of the same order as those for the kinetic and potential energies. However, the results indicate that the situation is not as problematic as is suggested by Winger *et al.*¹ Comparing the results obtained with the two different neighbourlist set-ups, it appears that the lack of energy conservation is mainly caused by the neglect of interactions from particles entering the cut-off distance in between neighbourlist updates. Switching to a more frequent update ($n_{\text{list}} = 5$ instead of 10) and a larger neighbour list ($r_{\text{list}} = 1.4$ vs. 1.2 nm) improves energy (and temperature) conservation significantly. The relative

fluctuations of the total energy remain smaller than 10% for time steps as large as 30 fs.

In almost all practical applications of molecular dynamics, simulations are performed at constant temperature, rather than constant energy. Our results obtained for the NpT ensemble show that coupling to a thermostat effectively compensates for the flow of energy into or out of the system due to integration errors. Even for time steps as large as 50 fs, the average system temperature remains close to the target temperature (within ~ 1 K). Even better temperature control can be achieved by reducing the temperature coupling constant τ_T from 1 to 0.1 ps, although with such tight coupling (τ_T approaching the time step) one can no longer speak of a weak-coupling scheme. The averaged squared value of the temperature coupling parameter λ , a measure of the energy pumped into the system, is close to its ideal value of 1 in all of our simulations. Cooling by more than 20 K, as reported by Winger *et al.*,¹ is not observed. Note that the system sizes, simulation times and other simulation parameters were chosen similarly. Note also that cooling, rather than heating which usually arises from integration errors, is observed in our systems (*cf.* Tables 1 and 2) only when the pairlist cut-off equals the cut-off of the interaction potential at 1.2 nm. In this case, the potential energy gain due to particles that enter the cut-off distance in-between neighbourlist updates is neglected, causing the overall cooling of the system. Switching to an update frequency of $n_{\text{list}} = 1$ removes this effect, leading to similar results as obtained with an enlarged pairlist cut-off. In the GROMOS implementation³ of the MARTINI force field, the neighbourlist cut-off equals the cut-off of the interaction potential, both at a distance of 1.4 nm. We tested this set-up also with GROMACS, and indeed a cooling effect was observed; however, the degree of cooling is comparable to the results for the set-up with the 1.2 nm cut-off (see Tables 1 and 2) and much less than in the study of Winger *et al.*¹

Upon a close inspection of the respective codes, we found that the apparent strong cooling reported by Winger *et al.*¹ is a consequence of the way in which GROMOS codes⁴ calculate the temperature at full times. As is detailed in the ESI,[†] it is clear that the reported temperature at full times in GROMOS does not reflect the instantaneous temperature of the system.

Table 2 Properties of pure water and hexadecane systems in the NpT ensemble. Results obtained from 1.2 ns simulations, analyzed over the last 600 ps. Temperature and pressure were coupled to 300 K and 1 bar, with a coupling constant of 1 ps and 5 ps, respectively. The effect of time step dt , pairlist update frequency n_{list} , and pairlist cut-off r_{list} on selected properties (ensemble averages of the temperature T , total potential energy E_{pot} , and the squared temperature scaling factor λ) is presented

dt/fs	n_{list}	$r_{\text{list}}/\text{nm}$	Water, NpT			Hexadecane, NpT		
			$\langle T \rangle/\text{K}$	$\langle E^{\text{pot}} \rangle/\text{kJ mol}^{-1}$	$\langle \lambda^2 \rangle$	$\langle T \rangle/\text{K}$	$\langle E^{\text{pot}} \rangle/\text{kJ mol}^{-1}$	$\langle \lambda^2 \rangle$
	10	1.2						
12			299.8	−45324	1.0000	299.9	−47162	1.0000
40			298.8	−45446	1.0001	298.6	−47322	1.0002
40 ^b			299.9	−45368	1.0001	299.9	−47256	1.0001
50			298.8	−45500	1.0002	298.4	−47432	1.0002
	5 ^a	1.4						
40			300.0	−45391	1.0000	300.0	−47254	1.0000
50			300.3	−45419	1.0000	300.1	−47267	1.0000
40 ^c			299.9	−45745	1.0000	299.9	−47836	1.0000

^a Similar results are obtained with $n_{\text{list}} = 10$, $r_{\text{list}} = 1.4$ and with $n_{\text{list}} = 1$, $r_{\text{list}} = 1.2$. ^b Simulation with $\tau_T = 0.1$ ps. ^c GROMOS type implementation³ in which the potential is shifted between 0.0 and 1.4 nm.

Within the Leap-frog scheme that both GROMACS and GROMOS codes use, the GROMACS codes implement the calculation of the temperature at full times from the *average kinetic energies* at half times, which uses the known velocities at half times. GROMOS codes, in contrast, implement the calculation of the temperature at full times from the kinetic energy at full times, using the *average velocities* at half times. It is easily shown that the reported temperature is systematically lower than the instantaneous temperature when using the latter definition. This effect becomes larger as the time-step increases, leading to an apparent, but misleading, cooling effect in simulations performed using GROMOS. The issue of the calculation of velocity-dependent properties in the Leap-frog scheme is also discussed by Cuendet and van Gunsteren,⁹ with the suggestion to use the average kinetic energy (as implemented in GROMACS) rather than the average of the velocities (GROMOS) in MD simulation. A similar problem is noted with CHARMM,¹⁰ reporting a temperature that does not reflect the actual temperature in simulations when using large time-steps (see ESI for details).

Based on the two arguments discussed above, we conclude that time steps exceeding 10 fs can be used in the MARTINI force field, and possibly also in combination with other CG force fields that use a similar degree of coarse-graining. Whereas one can debate the first argument (*i.e.* the ‘idealistic’ *versus* ‘pragmatic’ view of the power of CG simulations), the second argument (*i.e.* the insensitivity of both structural and thermodynamic properties to the magnitude of the time step) implies that a reduction of the time step to 10 fs or below is a waste of computer time. Nevertheless, we agree that time steps of 40 fs and beyond are pushing the limits too far. We therefore recommend a time step of 20–30 fs, in combination with an enlarged pairlist cut-off (to 1.4 nm) to be on the safe side. Of course, one should always check whether or not results are biased by the choices made. Given that the largest simplifications are made at the level of the interaction potentials, this can best be done by comparing to results obtained using more detailed models.

An additional point raised by Winger *et al.*¹ is their observation of freezing of the MARTINI water at 300 K, which would make it less suitable for biomolecular applications. The unwanted freezing of water has already been observed and discussed in our previous work.² Here, we would like to raise the following points: (i) although the LJ parameters for water ($\epsilon = 5.0 \text{ kJ mol}^{-1}$, $\sigma = 0.47 \text{ nm}$) bring it into the solid state region of the LJ phase diagram, the use of a shift potential reduces the long-range attractive part. Consequently, the CG water is more fluid compared to the standard LJ particle. In fact, we almost never observed freezing in the simulations reported in Tables 1 and 2, even in simulations extended to 12 ns. In the GROMOS implementation of MARTINI, a modified potential is used that is slightly longer ranged (reflected, for instance, by the lower potential energies for this model, see Table 2). This might explain the more rapid freezing of water observed by Winger *et al.*;¹ (ii) We have

previously⁸ determined the freezing temperature of the CG water as $290 \pm 5 \text{ K}$ (see also ESI). While this is admittedly higher than it should be, in most applications freezing is not observed as long as no nucleation site is formed. Apart from simulations performed at lower temperatures, rapid freezing is therefore a potential problem in systems where a nucleation site is already present (a solid surface, but also an ordered bilayer surface may act as one) or when periodicity enhances the long range ordering (*e.g.*, for small volumes of water). (iii) In cases where the freezing poses a problem, a simple pragmatic solution has been presented in the form of antifreeze particles.² This situation is clearly not ideal, and there is certainly room for improvement. In future versions of the MARTINI force field we intend to use a softer potential with a tuneable width to extend the fluid range of the water model.

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